DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/21/10 has been entered.

2. Claims 1, 5-8, 10-14 and 18-25 are all the pending claims for this application.

3. Claims 5 and 12 were amended in the Response of 9/21/10.

4. Claims 18-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. The non-elected species of antibody of Claim 14 are withdrawn.

5. Claims 1, 5-8, and 10-14 are the pending claims under examination with elected species to TRAIL-R2 (Claim 11) and SEQ ID NO: 8 (Claim 14).

6. This Office Action contains new grounds for rejection.

Information Disclosure Statement

7. The IDS' of 9/21/10, 11/18/10, 6/13/11 and 8/3/11 have been considered and entered. The initialed and signed 1449 forms are attached.

Withdrawal of Objections

Sequence Listing

8. The objection to the Sequence Listing filed 2/26/10 for the reasons set forth on the attached Raw Sequence Listing report and the Notice of Sequence Non-Compliance is withdrawn in view of the revised Sequence Listing filed 9/21/10.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, first paragraph

Scope of Enablement

9. The rejection of Claims 1, 5-8, and 10-14 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for using any antibody to induce apoptosis in any cell much less a cancer cell expressing TRAIL receptor whether in vireo or in vivo is withdrawn.

Applicants allegations on p. 5 of the Response of 9/21/10 have been considered and found persuasive. Applicants allege Claim 12 as amended now recites "a cell expressing the TRAIL receptor". Generic claim 1 relates to an antibody that recognizes a TRAIL receptor having a cytoplasmic death domain. The Examples of the present application demonstrate that the antibodies recognizing a TRAIL receptor of the present invention induce apoptosis in a cell expressing the TRAIL receptor (see, in particular,

page 40, line 34 to page 42, line 20). Thus, the specification provides enablement for using the antibodies recognizing the TRAIL receptor, which are recited in claims 1, 5-8, and 10-14, to induce apoptosis in a cell expressing the TRAIL receptor.

Claim Rejections - 35 USC § 102

10. The rejection of Claims 1, 5-8, and 10-13 under 35 U.S.C. 102(b) as being anticipated by Miller et al. (WO 01/77342; published 10/18/01; cited in the IDS of 9/30/08) is withdrawn.

Applicants allegations on pp. 5-6 of the Response of 9/21/10 have been considered and found persuasive. The instant claims exclude the presence of the CL domains of Miller.

Rejections Maintained

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. The rejection of Claims 10 and 14 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The rejections were set forth in the Office Action of 4/6/10 as follows:

"a) Claim 10 is rejected because it is drawn to a limitation outside of the scope for the antibody recited in Claim 1. The antibody of claim 1 and dependent claims thereof is

required to be at least a trimer or triabody, but dependent Claim 10 requires two scFv molecules which is technically a dimer or diabody.

b) Claim 14 is rejected because it is drawn to a limitation outside of the scope for the antibody recited in Claim 1. The antibody of claim 1 and dependent claims thereof is required to be at least a trimer or triabody, but dependent Claim 14 requires a dimer (a tandem diabody) of an antibody with the amino acid sequence shown in SEQ ID NO: 8."

Applicants allege of pp. 6-7 of the Response of 9/21/10 Claim 10 specifies that the antibody comprises two sc(Fv)2 molecules which have four Fv units (see page 13, line 35 to page 14, line 1 of the specification). Since claim 1 requires the antibody to have at least three Fv units, claim 10 is clearly within the scope of claim 1.

Claim 14 specifies that the antibody to comprise the amino acid sequence of SEQ ID NO: 2, 4, 6, or 8. SEQ ID NO: 2 (ScFvH2L), 4 (ScFvHIL), and 6 (ScFvHOL) are triabodies with three Fv units (see page 33,lines 13-16 of the specification). SEQ ID NO: 8 is a tandem diabody which has four Fv units (see page 15, lines 32-35). Since claim 1 requires the antibody to have at least three Fv units, claim 14 is clearly within the scope of claim 1.

Response to Arguments

The examiner has maintained the rejection because the specification defines an "Fv unit" as follows:

"…For example, of the antibody fragments described above, "Fv" is a minimal antibody fragment comprising the complete antigen recognition and binding sites. *"Fv" is a dimer (VH-VL dimer) consisting of one unit of VH and one unit of VL* bound very strongly by non-covalent bonding. The three complementarity determining regions (CDRs) of each variable region interact with each other, thereby forming an antigen binding site on the surface of the VH-VL dimer. Six CDRs confer an antigen binding site to the antibody." (p. 12, lines 18-24)

Thus the examiner submits that generic Claim 1 requires that there be “at least three “Fv units”. For any given scFv dimer (or two scfv molecules or two VH/VL pairings), there are two (2) "Fv units" by the definition provided in the specification, resulting in less than the required "at least three Fv units." According to the definition then “at least three Fv units” would have three (3) VH/VL pairings.

The rejection is maintained.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

12. Claims 1, 5-8 and 10-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 5-8 and 10-14 are drawn to the genus of antibodies comprising at least one linker and at least three Fv units (VH/VL pair) wherein i) the antibody recognizes any TRAIL receptor comprising a cytoplamic death domain; ii) the antibody induces apoptosis in any cell expressing the any TRAIL receptor; iii) the antibody induces

apoptosis in any cancer cell expressing the any TRAIL receptor; and where the preferred TRAIL receptor is TRAIL-R2; and a preferred species of antibody is of SEQ ID NO:8.

It is the examiner's position that the specification and art does not support the myriad antibodies encompassed by the scope of the claims.

Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised Mar 28, 2008), the claimed invention must meet the following criteria as set forth.

a) Actual reduction to practice: The working examples of cytotoxic, apoptosis-inducing TRAIL-R2 antibodies are described in Section 4 (pp. 40-41) of the specification:

The data for cytotoxic activity of TRAIL-R2 diabodies on COLO 205 cancer cells in vitro are shown in Fig. 1. The cell count did not decrease after addition of the diabody alone, suggesting that the diabody has no cytotoxic activity by itself, and cytotoxic activity was detected when M2 antibody was added to crosslink the diabody. This suggests that apoptotic signals are transmitted when the polymerization of TRAIL receptor on the surface of cell membranes is enhanced.

The data for cytotoxic activity of TRAIL-R2 triabodies on COLO 205 cancer cells in vitro are shown in Fig. 2. The results showed that neither the diabodies nor whole IgG had marked cytotoxic activity. In contrast, the cell count was dramatically decreased after addition of the triabody, suggesting that the triabody had obvious cytotoxic activity with the activity significantly higher when the triabody had the 1-mer or O-mer linker.

The data for cytotoxic activity compared between the triabody and tandem diabody on COLO 205 cancer cells in vitro are shown in Fig. 3. This result showed that the activity of the tandem diabody was stronger than that of the triabody, and was equivalent to or greater than that of the natural ligand Apo2L. These results suggest that of the molecules tested, the tandem diabody by itself is the most effective molecule in inducing apoptosis.

The antibody of SEQ ID NO:8 is supported as showing a cytotoxic effect on TRAIL-R2-expressing cells but just any TRAIL-R-expressing cell. Applicants have not

demonstrated that the antibody of SEQ ID NO:8 would recognize any TRAIL-R having a cytoplasmic death domain much less expressed on any cancer cell wherein the antibody of SEQ ID NO:8 would induce apoptosis.

b) Disclosure of drawings or structural chemical formulas: the specification and drawings do not show that applicant was in possession of the myriad antibodies against any TRAIL-R (Claim 1) much less the TRAIL-R2 species and having the structure/function correlation required of the claimed antibody.

c) Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with *correlation between structure and function* for the genus of the myriad antibodies against any TRAIL-R (Claim 1) much less the TRAIL-R2 species and having the structure/function correlation required of the claimed antibody.

d) Method of making the claimed invention: the specification teaches making scfv antibodies and screening the antibody for functional apoptotic activity.

e) Level of skill and knowledge in the art: the cloning of antibody DNA, construction of scfv antibody from VH/VL domains, protein sequencing, protein expression and bioassays for identifying functional antibodies was well established at the time of the invention.

f) Predictability in the Art: It has been well known that minor structural differences even among structurally related compounds can result in substantially different binding

activities for the same antibody. For example, Lederman et al (Molecular Immunology 28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other activities when constructing analogs (see entire document). Accordingly, Applicants most generic claim is drawn to any TRAIL-R known and yet to be discovered with the proviso the TRAIL-R contain a cytoplasmic death domain. Thus, in the absence of Applicants showing more than the example of the antibody of SEQ ID NO:8 binding to TRAIL-R2 in cells induced to undergo apoptosis, the skilled artisan could reasonably conclude that Applicants were not in possession of the full scope of antibodies against the full scope of TRAIL-R at the time of filing.

Adequate written description for an antibody appears to hinge upon whether the specification provides adequate written description for the antigen. While a specification may enable making a genus of antibodies, this does not necessarily place applicant in possession of the resultant antibodies (See *In re Kenneth Alonso* October (Fed. Cir. 2008) sustaining a lack of adequate written description rejection where “the specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies” where the specification does not characterize the antigens to which the monoclonal antibodies must bind). Again, where Applicants most generic claim (Claim 1) is drawn to any TRAIL receptor without reference to structure or function of the protein, the ordinary artisan could reasonably conclude that Applicants were not in possession of the full

scope of antibodies meeting the full scope of TRAIL-R at the time of filing.

Applicants have failed to show the existence of appropriate genus of TRAIL-R having a cytoplasmic death domain much less the genus of antibodies binding to the genus of antigens and also having the claimed functional properties required of the antibody. The Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d 1886,1895 (Fed. Cir. 2004).

The problem here is that the instant specification fails to provide a disclosure of which antibody retains the appropriate antibody specificity for any TRAIL-R having a cytoplasmic death domain and further being able to induce apoptosis in any cancer cell expressing any one of the myriad TRAIL-R. A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus of TRAIL-R much less the antibodies that exhibit the required functional properties for each of the claimed elements. There is insufficient guidance and direction as to the written description of the claimed antibody, as broadly encompassed by the claimed invention for any TRAIL-R having a cytoplasmic death domain. Given the well-known high level of polymorphism of immunoglobulins / antibodies, the skilled artisan would not have been in possession of the vast repertoire of antibodies and the unlimited number of antibodies encompassed by the claimed invention; one of skill in the art would

conclude that applicant was not in possession of the functional attributes of a representative number of species possessed by the members of the genera of ant-TRAIL-R antibodies as indicated above, and broadly encompassed by the claimed invention. One of skill in the art would conclude that the specification fails to disclose a representative number of species much less a single species to describe the claimed genera.

Applicants have not characterized a sufficient number of TRAIL-R having a cytoplasmic death domain much less reduced to practice a reasonable number of antibodies consisting of at least one linker and at least three Fv units which bind to those TRAIL-R, much less possess the functional attributes required of the antibodies and therefore, the ordinary artisan could reasonably conclude that Applicants were not in possession of the claimed genus of antibodies meeting all of the structural and functional properties required of the claims.

Conclusion

13. No claims are allowed

14. The antibody sequence of SEQ ID NO:8 is free from prior art.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Primary Examiner
Art Unit 1643